PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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DANEMARK

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	17.02.2005

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
IPB/129455	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB 03/05429	26.11.2003	26.11.2002

Applicant
BIONATURE E.A. LIMITED et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

   The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

   Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

   For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

   The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference IPB/129455	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IB 03/05429	International filing date *(day/month/year)* 26.11.2003	Priority date *(day/month/year)* 26.11.2002
International Patent Classification (IPC) or both national classification and IPC A61K45/00, A61K38/22, A61K31/506, G01N33/68, A61P29/00		
Applicant BIONATURE E.A. LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
14.05.2004	17.02.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Winger, R Telephone No. +49 89 2399-8129

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB 03/05429

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-31 as originally filed

Claims, Numbers

1-14 received on 17.11.2004 with letter of 15.11.2004

Drawings, Sheets

1/10-10/10 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-14 (partly)

because:

☒ the said international application, or the said claims Nos. 1-3 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-14 (partly)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-14
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-14
Industrial applicability (IA)	Yes:	Claims	4-14
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Section III

1. Claims 1-3 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

2. The International Search Report has been carried out only for those parts of the claims relating to identified compounds (antalarmin and urocortin). Accordingly, the International Preliminary Examination is established with respect to those (parts of the) claims relating to matter which has been searched.

Re Section V

3. Prior Art: Reference is made to the following documents cited in the International Search Report
   - D1: INFECTION AND IMMUNITY, vol. 70, no. 11, 2002-11, pages 6068-6074
   - D2: AMERICAN JOURNAL OF PHYSIOLOGY (ENDOCRINOLOGY AND METABOLISM), vol. 275, no. 5 part 1, 1998-11, pages E757-E762
   - D3: PEPTIDES, vol. 21, no. 12, 2000-12, pages 1799-1809
   - D4: JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 277, no. 14,2002-04-05, pages 12280-12287
   - D5: JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, vol. 88, no. 1, 2003-01, pages 478-483

3.1 Document D1 discloses that CRH enhances LPS-induced TNF-α, IL-1 and IL-6 production in the RAW264.7 monocyte/macrophage cell line and that the synthetic CRH-R1 antagonist antalarmin suppresses the pro-inflammatory cytokine production by macrophages. In vivo tests are disclosed, where antalarmin prolonged survival of mice subjected to LPD-induced septic shock.

3.2 Document D2 discloses that synthetic rat urocortin has anti-inflammatory activities and reduces LPS-induced serum TNF-α and IL-1 levels in mice. UCN also has a direct inhibitory effect on LPS-induced TNF in rat Kupffer cells, which constitute the main macrophage population.

3.3 Document D3 discloses CRF-R1 and CRF-R2-α are mainly expressed in lamina propria mononuclear cells (consisting of lymphocytes, monocytes and macrophages), which suggests that agonists (CRF/urocortin) to these receptors may act directly on lamina

propria inflammatory cells, such as monocytes/macrophages. A possible role of UCN in inflammatory regulation is suggested.

3.4 Document D4 discloses that CRH induces apoptosis mediated by CRH-R1 and is blocked by its antagonist antalarmin.

3.5 Document D5 discloses urocortin (not CRH) is detected in biopsies of normal and inflamed gastric mucosa, where it may exert an antiinflammatory effect. Assuming the priority to be validly claimed, document D5 does not constitute prior art for the International Preliminary Examination.

4. Novelty (Article 33(2) PCT):

Claim 1 relates to the use of CRH-R1 synthetic antagonists and/or CHR-R2 agonists for the treatment of inflammatory disease associated to activation, deactivation, differentiation and apoptosis of macrophages, claims 4 and 13 relate to the corresponding pharmaceutical compositions and kits and claim 11 to the second medical use. It is noted that in the description synthetic is defined as manufactured using technical processes such as recombinant technology, i.e., natural compounds recombinantly produced are not considered to be excluded. As macrophages are involved in virtually all inflammatory diseases, this restriction is not considered to be delimiting.

As documents D1 and D2 disclose such therapeutic application (in vivo), the subject-matter of claims 1-14 does not seem to be novel. The pharmaceutical compositions and kits are additional anticipated by documents D3 and D4.

5. Inventive Step (Article 33(3) PCT):

Notwithstanding aforementioned lack of novelty, the subject-matter would not seem to be inventive, as the role of CRH-R1 antagonist and CHR-R2 agonists in inflammatory disorders is suggested in documents D3 and D4.

PATENT CLAIMS

1. Use of one or more synthetic CRH-R1 antagonists and /or CRH-R2 agonists for the treatment of an inflammatory disease or condition associated to activation, deactivation, differentiation and apoptosis of macrophages.

2. Use according to claim 1, wherein the one or more synthetic CRH-R1 antagonists and/or CRH-R2 agonists comprises antalarmin.

3. Use according to claim 1 or 2, wherein the inflammatory disease or condition is chronic inflammatory bowel disease, idiopathic inflammatory disorder, inflammatory disorders of connective tissues, inflammatory demyelinating polyneuropathies, inflammatory myopathies, inflammatory diseases of joints including bursitis, the fibromyalgia syndrome and inflammatory diseases of upper gastrointestinal tract.

4. Pharmaceutical composition comprising one or more synthetic CRH-R1 antagonists and /or CRH-R2 agonists.

5. Pharmaceutical composition according to claim 4, wherein the composition is formulated for local or systemic administration.

6. Pharmaceutical composition according to claim 4 or 5, wherein the composition further comprises usual exhibients such as diluents, fillers, binders, disintegrants, lubricants, conserving agents, flavourings and colourings.

7. Pharmaceutical composition according to any of the claims 4 to 6, wherein the formulation is formulated for oral, parenteral or intradermal administration.

8. Pharmaceutical composition according to claim 7, wherein the composition is formulated as an injection liquid.

9. Pharmaceutical composition according to any of the claims claim 4 to 8, wherein the one or more synthetic CRH-R1antagonist and/or CRH-R2 agonist comprises antalarmin.

10. Pharmaceutical composition according to claim 9, wherein the one of more synthetic CRH-R1 antagonist and/or CRH-R2 agonist is antalarmin.

11. Use of one or more synthetic CRH-R1 antagonists and /or CRH-R2 agonists for the manufacture of a pharmaceutical composition for the treatment of an inflammatory disease or condition associated to activation, deactivation, differentiation and apoptosis of macrophages.

12. Use according to claim 11, wherein the inflammatory disease or condition is chronic inflammatory bowel disease, idiopathic inflammatory disorder, inflammatory disorders of connective tissues, inflammatory demyelinating polyneuropathies, inflammatory myopathies, inflammatory diseases of joints including bursitis, the fibromyalgia syndrome and inflammatory diseases of upper gastrointestinal tract.

13. Kit intended for the treatment of an inflammatory disease or condition comprising one or more CRH-R1 antagonists and /or CRH-R2 agonists comprised in one of more individual pharmaceutical compositions.

14. Kit according to claim 13, wherein the one or more CRH-R1 antagonists and/or CRH-R2 agonists comprises antalarmin.